Safety of Tenofovir Disoproxil Fumarate (TDF) for Pregnant Women facing the COVID-19 Pandemic

Sonia Hernandez-Diaz, Brian T. Bateman, Loreen Straub, Yanmin Zhu, Helen Mogun, Michael Fischer, and Krista F. Huybrechts

Correspondence to Dr. Sonia Hernandez-Diaz, Department of Epidemiology, Harvard T.H. Chan School of Public Health, 677 Huntington Avenue. Boston, MA 02115 (e-mail: shernan@hsph.harvard.edu)

Authors affiliations: Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, United States (Sonia Hernandez-Diaz). Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, United States (Brian T. Bateman, Loreen Straub, Yanmin Zhu, Helen Mogun, Michael Fischer, and Krista F. Huybrechts). Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, United States (Brian T. Bateman).

Funding: The study was supported by internal funds of the Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Harvard Medical School. Drs. Bateman, Hernandez-Diaz and Huybrechts are supported by the National Institute of Mental Health (R01 MH116194), the National Institute on Drug Abuse (R01 DA044293, R01 DA049822), and the National Institute of Child Health and Human Development (R01 HD097778).

Conflict of interest: Sonia Hernandez-Diaz reports being an investigator on grants to her institution from Takeda for unrelated studies; personal fees from UCB and Roche outside the submitted work; and having served as an epidemiologist with the North America AED pregnancy registry, which is funded by multiple companies. Brian T. Bateman received research grants to Brigham and Women's Hospital from Eli Lilly, Baxalta, and Pacira for unrelated studies; personal fees from Aetion and from Alosa Foundation outside the submitted work; and served on an expert panel for a postpartum hemorrhage quality improvement project that was conducted by the Association of Women's Health, Obstetric, and Neonatal Nurses and funded by a grant from Merck for Mothers. Michael Fischer received a research grant to Brigham and Women's Hospital from Surescripts for unrelated studies and personal fees from Alosa Foundation outside the submitted work. Krista F. Huybrechts received research grants to Brigham and Women's Hospital from Eli Lilly for unrelated studies. The remaining authors report no potential conflict of interest.

Data Availability: The data underlying this article are available through Centers for Medicare and Medicaid Services (CMS) conditional on data use agreements and fees.

Running head: Tenofovir Safety in Pregnancy.

ABSTRACT

We assessed the teratogenicity of tenofovir, a human immunodeficiency virus (HIV) drug similar to remdesivir currently being evaluated for the treatment of coronavirus disease 2019 (COVID-19). Using US Medicaid Analytic Extract (MAX) claims data (2000-2014), we identified a population-based pregnancy cohort of women with HIV who filled ≥1 prescription for antiretroviral therapies (ART) during the first trimester. Women on tenofovir disoproxil fumarate (TDF) were compared with women receiving ART without TDF. Major malformations were identified by ICD-9 codes using validated algorithms. Relative risks (RR) and 95% confidence intervals (CI) were estimated using propensity score (PS) stratification to control for potential confounders. We incorporated the results into prior knowledge by conducting a systematic literature review and a meta-analysis. Major congenital malformations were diagnosed in 37 out of 866 (4.27%) infants exposed to TDF and 38 out of 1,020 (3.73%) infants exposed to ART other than TDF; the adjusted RR was 1.21 (95% CI 0.77 to 1.90). Estimates for specific malformations were imprecise. The pooled RR from the meta-analysis with six prior studies was 0.88 (0.75 to 1.03). Based on evidence accumulated in patients with HIV, first trimester TDF use does not increase the risk of major congenital malformations overall in the newborn compared to other ART.

KEY WORDS

Tenofovir, TDF, pregnancy, malformations, HIV, COVID-19

ABBREVIATIONS

ART: antiretroviral therapies
CI: Confidence intervals
COVID-19: Coronavirus disease 2019
HIV: Human immunodeficiency virus
LMP: Last menstrual period
MAX: Medicaid Analytic Extract
PS: propensity score

RR: Relative risks
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2
TDF: Tenofovir disoproxil fumarate

Worldwide, as of the end of 2020, over one hundred million women had been pregnant since the Coronavirus Disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) started.[1] Pregnant women are susceptible to SARS-CoV-2 infection and may have a higher risk to develop severe COVID-19 if infected than non-pregnant women of the same age.[2-5] Cases of maternal death in pregnant women with COVID-19 have been reported.[6] Moreover, severe COVID-19 may increase the risk of prematurity and other adverse obstetric or neonatal outcomes,[2,4,7,8] and vertical transmission cannot be completely ruled out.[2-4,9-11] Therefore, many pregnant women and their physicians confront the decision of whether to use treatments for COVID-19.

By September 2020, tenofovir had emerged as a promising therapy for SARS-CoV-2 infection. Molecular docking and extension reaction studies suggest that remdesivir, tenofovir and other nucleoside reverse transcriptase inhibitors may be effective against SARS-CoV-2 by inhibiting its RNA polymerase, as long as they attain high intracellular concentration at target tissues.[12-14] Ferret infection models have shown that tenofovir-emtricitabine reduces SARS-CoV-2 titers in nasal washes.[15] In observational studies, human immunodeficiency virus (HIV)-positive patients receiving tenofovir disoproxil fumarate (TDF)-emtricitabine had an up to 50% lower risk for COVID-19 diagnosis and related hospitalization.[16-18] Tenofovir is currently being evaluated in controlled randomized clinical trials for both treatment and prophylaxis of COVID-19.[19] Given the promising clinical trials results for remdesivir,[20,21] tenofovir is expected to be effective since the two drugs are in the same family of medications. A key difference between these drugs is that tenofovir can be administered orally, whereas remdesivir requires daily intravenous infusion.

While there is no evidence regarding the safety profile in pregnancy for many of the treatments currently being evaluated for COVID-19, including remdesivir, some data exist for tenofovir based on its use for the treatment of HIV infection and, to lesser extent, for Hepatitis B virus infection. It is therefore important to obtain and communicate

reliable information about the safety of tenofovir, including teratogenicity, before pregnant populations are exposed on a broad scale. We reviewed the literature and evaluated the risk for major congenital malformations associated with early in pregnancy exposure to tenofovir as HIV treatment using a large healthcare utilization database.

METHODS

Study population

We conducted a cohort study of pregnancies nested in the Medicaid Analytic eXtract (MAX; January 1, 2000 to December 31, 2014), which includes enrollment information and healthcare claims for Medicaid beneficiaries nationwide in the United States. The development of the linked mother-infant pregnancy cohort has been described previously.[22] Briefly, women with a code indicating delivery were identified and linked to live-born infants based on shared family case numbers. Women were required to be continuously enrolled in Medicaid, without supplementary private insurance or restricted benefits, for 3 months prior to the estimated date of last menstrual period (LMP) through 1 month after delivery, and infants were required to be insured from birth until 3 months thereafter, unless they died sooner. Pregnancies with exposure to a known teratogenic medication (i.e., warfarin, antineoplastic agents, lithium, isotretinoin, misoprostol, thalidomide) during the first trimester and pregnancies with a chromosomal abnormality were excluded.

The study population was restricted to women with a recorded diagnosis of HIV between 3 months prior to LMP and delivery (see Web Table 1 for diagnostic and procedure codes).[23] Since infants exposed to antiretroviral therapies (ART) in the first trimester have been reported to have slightly higher risk of malformations than those exposed later in pregnancy,[24-27] we further restricted the cohort to pregnancies exposed to ART during the first trimester, defined by at least one dispensing of an antiretroviral medication between LMP and 3 months after LMP.

Exposure

Women were considered exposed if they filled at least one prescription for TDF (the tenofovir formulation available during the study period) during the first trimester of pregnancy. The reference group was comprised of pregnant women who received ART that did not include any dispensings of TDF from 3 months before LMP through the end

of the first trimester to reduce the probability of exposure during early pregnancy from use of TDF dispensed before the start of pregnancy.

Use of three-drug ART regimes has been the standard of care during pregnancy as it reduces the risk of perinatal HIV transmission to less than 1%.[28,29] During the study period, HIV patients on TDF most often received it with emtricitabine plus an integrase inhibitor, a protease inhibitor, or a nonnucleoside reverse transcriptase inhibitor.[30,31] Therefore, we also present results for the TDF-emtricitabine combination (the combination for which the decrease in risk of COVID-19 related hospitalization had been reported in the observational study)[16,17] and accounted for the other antiretrovirals dispensed during the first trimester in the analyses by balancing on the number of distinct ART drugs in the regime using the propensity score. Note that the combination TDF-emtricitabine has been recommended in the US for pre-exposure prophylaxis in women only after the study period.

Outcomes

The outcome of interest was a composite measure of all major congenital malformations because the number of exposed women was too small to evaluate specific malformations. The presence of malformations was defined using validated algorithms based on inpatient or outpatient diagnoses and procedures, which have been shown to identify the outcomes with high positive predictive values (75% to 98%).[32-35] (See Web Table 2)

Covariates

Potential confounders and proxies for confounders considered included maternal sociodemographic characteristics (e.g., state of residence, age, race/ethnicity), markers of HIV disease severity (e.g., infections), comorbid medical conditions (e.g., diabetes, hypertension), other prescription drugs dispensed (e.g., antimicrobials), and general markers of the burden of illness (Table 1 for a comprehensive list).

Analyses

Propensity scores (PS) were calculated using a logistic regression model that estimated the probability of being dispensed TDF in the first trimester based on confounder values. A separate model was created for TDF-emtricitabine. All variables listed in Table 1 were included in the PS, except for the specific ART medications. After trimming observations from the non-overlapping regions of the PS distribution, we created 50 equally sized PS-

strata based on the distribution among the treated women.[36] In the outcome models, the reference observations were weighted using the distribution of the TDF-treated among PS-strata. Baseline characteristics and total number of antiretrovirals prescribed during the first trimester were compared between exposed and reference groups, before and after PS stratification. The risk of major malformations was summarized in the full and stratified samples. Relative risks (RR) with their 95% confidence intervals (CI) were estimated using generalized linear models.

The research was approved by the institutional review board of Brigham and Women's Hospital, which waived the need for informed consent.

Literature review

We conducted a systematic review and meta-analysis for studies that examined the relationship between use of TDF early in pregnancy and overall congenital malformations. We searched MEDLINE via PubMed and additionally did a Google-engine based web search for abstracts with terms related to "tenofovir", "birth defect/malformation" and "pregnancy". The references cited in all included studies were reviewed to identify additional eligible studies. Search criteria are described in detail in Web Table 3.

Articles were included if they were written in English and reported adequate information to calculate a RR for tenofovir exposure in the first trimester and congenital malformations. We excluded conference abstracts, animal studies, basic science research, case reports, case series, and commentaries. When reports were published on the same cohort, we only included the most recent publication to avoid duplication. We further restricted the meta-analysis to studies that had a comparison group that received ART.

Two authors (LS, SHD) screened the titles and abstracts of all identified articles according to the inclusion and exclusion criteria listed above. For articles passing the initial screen, the two authors independently performed full text review, finalized inclusion decisions, and extracted the relevant information using a standardized form. All discrepancies were resolved through discussion until reaching a consensus. A fixed-effects meta-analysis was performed, and results are reported in a forest plot. The I^2 metric (which represents the percentage of variance in meta-analysis that is attributable

to between-study heterogeneity) was computed to quantify between-study heterogeneity.

RESULTS

Study Population

The cohort included 872 pregnancies exposed to TDF during the first trimester and 1,033 exposed to ART that did not include TDF in the first trimester. Among TDF users, 743 received TDF-emtricitabine. Before PS stratification, there were some small differences in baseline characteristics between the exposure groups; women with first trimester TDF exposures were slightly older, more likely to be from the Northeast than from the South, had more infections, more trimethoprim prescriptions and more healthcare utilization, and received more antiretrovirals. The PS stratification procedure resulted in a sample of 866 women in the TDF and 1,020 in the comparator group. After adjustment through PS stratification, all covariates were well balanced including the number of distinct ART drugs. Specific ARTs were not included in the PS and were not expected to be balanced. (Table 1).

Tenofovir and Major Congenital Malformations

Before stratification, the prevalence of major congenital malformations was 4.24% for TDF exposed infants (37 events out of 872), 4.17% for infants exposed to TDF-emtricitabine specifically (31 events out of 743), and 3.68% for infants exposed to ART without TDF (38 events out of 1,033). The prevalence of major malformations after first trimester exposure was similar for the most common ART (Figure 1). Compared to infants exposed to other ART as a group, the unadjusted RR was 1.15 (95% CI, 0.74, 1.80) for TDF and 1.13 (95% CI, 0.71, 1.81) for TDF-emtricitabine (Table 2). After PS stratification, the prevalence of major congenital malformations was 4.27% for TDF exposed infants (37 events out of 866), 4.18% for infants exposed to TDF-emtricitabine specifically (31 events out of 741), and 3.73% for infants exposed to ART without TDF (38 events out of 1,020). Compared to infants exposed to other ART as a group, the adjusted RR for TDF was 1.21 (95% CI, 0.77, 1.90); it was 1.14 (95% CI, 0.71, 1.82) for TDF-emtricitabine. The most common malformations among TDF exposed infants were limb defects and genital defects, while for other ART they were cardiac and gastrointestinal. The small numbers did not allow estimation of RRs for specific defects.

Meta-analysis with Previous Studies

The Pubmed search yielded 27 citations of interest, of which 14 were directly identified as search hits, and 13 were identified based on sources cited in other search hits. All 27 identified studies underwent a full-text review, and results from 6 articles were included in the meta-analysis. Three additional citations were identified via the Google search strategy, of which none met the criteria described above to be included in the meta-analysis. While study designs varied between articles (Web Table 4), between-study heterogeneity was low (p-value for heterogeneity=0.346). Results from the meta-analysis indicated no increased prevalence of congenital malformations overall associated with TDF exposure during the first trimester compared to other ART without TDF. Since few studies provided adjusted estimates and the estimates did not change meaningfully with adjustment within those studies that did, we used crude RR estimates for the meta-analysis. The pooled RR not including the current study was 0.85 (95% CI 0.71, 1.00); upon including the current study it was 0.88 (95% CI 0.75, 1.03; Figure 2).

DISCUSSION

Principal Findings

Utilizing a large health care database of publicly insured individuals in the US from the years 2000 to 2014, we identified a nationwide cohort of pregnant women with HIV and estimated the relative prevalence of major congenital malformations in their newborns following exposure to TDF. Women who filled prescriptions for TDF, with or without emtricitabine, during the first trimester had a similar prevalence of malformations in their newborn than women with HIV who filled prescriptions for other ART that did not include TDF during the first trimester. However, based on this study alone, we could only exclude a two-fold increased risk. The study size was also too small to consider specific birth defects.

Literature Review

We incorporated the results from our analysis into existing knowledge by conducting a systematic literature review. Both the pooled RR from the meta-analysis and that estimated from the Medicaid cohort are consistent with a null finding for the impact of TDF on malformations, yet point estimates and upper limit of the 95% CI were quite different. The largest study was the Antiretroviral (ART) Pregnancy Registry, which reported a prevalence of congenital malformations for first trimester exposure of 2.8% for

ART overall (N=10,120), 2.4% for TDF (N=4,005), and 2.6% for emtricitabine (N=3,345). Their most recent report also included tenofovir alafenamide (N=233), approved for HIV treatment in the US since November 2015, with an estimated prevalence of malformations of 5.2% (2.7% to 8.8%).[37] Among the other studies, some estimated a slightly lower prevalence of malformations in infants with first trimester exposure to TDF,[26 27 38] while others found a slightly higher prevalence of malformations for TDF[24 25] than for other ART (Table 3). Relative risks for emtricitabine were uniformly null across studies. TDF has also been used for chronic Hepatitis B virus infection during pregnancy. Although the accumulated evidence is more limited than for HIV, it also suggests no significant increased risk of malformations associated with first trimester TDF exposure.[37,39]

We included only studies with internal active reference groups, hence minimizing confounding by HIV or associated comorbidities. Although the publications did not report adjusted relative risk estimates for the specific comparison of TDF versus other ART, residual confounding is expected to be modest given that our own estimate moved half a decimal point upon adjustment. Similarly, although some of the studies had substantial losses to follow up and others allowed retrospective enrollment, differential ascertainment of malformations by ART would be unlikely. Only two studies included stillbirths and elective terminations of pregnancy for fetal anomaly.[37,38] However, most terminations were for chromosomal anomalies and the relatively low number of stillbirths with malformations had little impact in the the results.

Although statistical testing did not suggest significant heterogeneity in RR estimates, when interpreting the results of the meta-analysis it is important to be aware of substantial diversity in the designs of the included studies. In addition to random error, heterogeneity in results may be due to a number of important differences, including outcome definitions (e.g., Metropolitan Atlanta Congenital Defects Program versus EUROCAT), internal study validity (e.g., amount of confounding control; though all studies restricted to women with HIV and ART therapy during the first trimester), or geographic differences (e.g. Europe versus United States). For example, the estimated prevalence of malformations for TDF exposed ranged from 2.4% to 8.9% across studies. Despite these differences, all relative risk estimates consistently fluctuated around the null.

Other pregnancy outcomes

Results must be interpreted alongside other safety findings related to TDF use in pregnancy. *In utero* TDF exposure has been linked to reduced infant bone mineral content,[40] although this effect has been refuted in a recent clinical trial.[41] Also, the PROMISE (Promoting Maternal and Infant Survival Everywhere) trial, conducted across multiple sites in sub-Saharan Africa and India, identified a potential safety concern for women randomized to receive TDF, emtricitabine, and ritonavir-boosted lopinavir. These participants were twice as likely to have infants born very prematurely (<34 weeks) or at very low birth weight (<1,500g), compared to women concurrently randomized to receive zidovudine, lamivudine, and ritonavir-boosted lopinavir.[29] Infants with *in utero* exposure to the TDF regime also had substantially greater risk of death within 14 days postpartum. However, these adverse birth outcomes were not elevated in two US-based cohort studies (the Surveillance Monitoring for ART Toxicities and International Maternal Pediatric Adolescent AIDS Clinical Trial Network P1025 studies).[31] Overall, the World Health Organization recommends TDF-based ART regimens as first-line therapy for all HIV-infected adults, including pregnant women,[42] and it is one of the most commonly used regimens among HIV-infected pregnant women in the US.[43]

Strengths and Limitations

This study is the second largest in terms of TDF exposed, thus meaningfully expanding the evidence. Moreover, it used real world evidence from a population-based sample (versus self-selected volunteers), used prospectively collected exposure information with respect to outcomes (versus inclusion of participants after prenatal screening), included an internal reference group (versus using as a reference for the risk of malformations estimations from external populations) and carefully reduced the possibilities of confounding inherent to observational studies by restricting to women on ART for HIV during the first trimester and further balancing characteristics through PS stratification.

In addition to these strengths, our study is also subject to certain limitations. First, we included only women with a live-born delivery because the diagnosis of malformations in abortions and stillbirths is incompletely recorded in healthcare utilization data. This approach may have resulted in the exclusion of pregnancies with the outcome, as fetuses with malformations are more likely to experience fetal death or termination. Therefore, the prevalence of major malformations at birth reported in this study could underestimate the risk in pregnant women. However, fetal losses would need to be unrealistically differential between women on different ART strategies to be a meaningful

source of selection bias.[44] Second, identification of major congenital malformations was based on diagnosis and/or procedure codes recorded in claims. While our algorithms to identify malformations have shown a high positive predictive value,[32-34] the potential for some misclassification remains. Misclassification would tend to bias relative risks towards the null unless it were differential among different ART strategies, which is unlikely. Third, information on TDF exposure is obtained from claims of filled prescriptions. Since some women may fill prescriptions for medications but not use them, our study may misclassify TDF unexposed pregnancies into the exposed group, thus underestimating any potential effect. However, women with HIV that filled their prescription are likely to use their drug to avoid vertical transmission. Fourth, while we required a diagnosis of HIV, if such codes were misapplied then it would be possible for some patients in our cohort to be using TDF as HIV pre-exposure prophylaxis. However, prophylaxis with TDF was approved by FDA in 2012 and recommendations for use in women came later, thus, this indication is unlikely for women who delivered before 2014. Moreover, our finding of increased infections and more antiretrovirals received by women in the TDF cohorts suggests that this was not a frequent occurrence. Fifth, we provide evidence for the safety of patterns of use in women with HIV, which could be different to that expected for COVID-19. However, at the same TDF doses, which virus triggered the indication is unlikely to modify teratogenic effects on the fetus. Fifth, the MAX dataset, along with most of the studies included in the meta-analysis, is an observational cohort, and there is always some potential for residual confounding, though this should be limited by the restriction to women with the indication, use of PS stratification and an active comparator group. Finally, the numbers were too small to assess specific malformation groups.

Conclusions

In conclusion, accumulated evidence suggests that first-trimester exposure to TDF in women with HIV does not increase the risk of major congenital malformations overall in the newborn compared to other antiretroviral treatment strategies. These findings are reassuring for pregnant women that may be eligible for TDF treatments in the context of the COVID-19 pandemic.

ACKNOWLEDGEMENTS

The study was supported by internal funds of the Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Harvard Medical School. Drs. Bateman, Hernandez-Diaz and Huybrechts are supported by the National Institute of Mental Health (R01 MH116194), the National Institute on Drug Abuse (R01 DA044293, R01 DA049822), and the National Institute of Child Health and Human Development (R01 HD097778). Sonia Hernandez-Diaz reports being an investigator on grants to her institution from Takeda for unrelated studies; personal fees from UCB and Roche outside the submitted work; and having served as an epidemiologist with the North America AED pregnancy registry, which is funded by multiple companies. Brian T. Bateman received research grants to Brigham and Women's Hospital from Eli Lilly, Baxalta, and Pacira for unrelated studies; personal fees from Aetion and from Alosa Foundation outside the submitted work; and served on an expert panel for a postpartum hemorrhage quality improvement project that was conducted by the Association of Women's Health, Obstetric, and Neonatal Nurses and funded by a grant from Merck for Mothers. Michael Fischer received a research grant to Brigham and Women's Hospital from Surescripts for unrelated studies and personal fees from Alosa Foundation outside the submitted work. Krista F. Huybrechts received research grants to Brigham and Women's Hospital from Eli Lilly for unrelated studies. The remaining authors report no potential conflict of interest. The data underlying this article are available through Centers for Medicare and Medicaid Services (CMS) conditional on data use agreements and fees.

REFERENCES

1. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *The New England journal of medicine.* 2020;382(8):727-733.
2. Chen H, Guo J, Wang C, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet.* 2020;395(10226):809-815.
3. Breslin N, Baptiste C, Gyamfi-Bannerman C, et al. COVID-19 infection among asymptomatic and symptomatic pregnant women: Two weeks of confirmed presentations to an affiliated pair of New York City hospitals. *Am J Obstet Gynecol MFM.* 2020:100-118.
4. Chen L, Li Q, Zheng D, et al. Clinical Characteristics of Pregnant Women with Covid-19 in Wuhan, China. *The New England journal of medicine.* 2020;382(25):e100.
5. Zambrano LD, Ellington S, Strid P, et al. Update: Characteristics of Symptomatic Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status - United States, January 22-October 3, 2020. *MMWR Morbidity and mortality weekly report.* 2020;69(44):1641-1647.
6. Ellington S, Strid P, Tong VT, et al. Characteristics of Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status - United States, January 22-June 7, 2020. *MMWR Morbidity and mortality weekly report.* 2020;69(25):769-775.
7. Qiao J. What are the risks of COVID-19 infection in pregnant women? *Lancet.* 2020;395(10226):760-762.
8. Zhu H, Wang L, Fang C, et al. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. *Transl Pediatr.* 2020;9(1):51-60.
9. Fan C, Lei D, Fang C, et al. Perinatal Transmission of 2019 Coronavirus Disease-Associated Severe Acute Respiratory Syndrome Coronavirus 2: Should We Worry? *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2021;72(5):862-864.
10. Dong L, Tian J, He S, et al. Possible Vertical Transmission of SARS-CoV-2 From an Infected Mother to Her Newborn. *JAMA : the journal of the American Medical Association.* 2020;323(18):1846-1848.
11. Zeng H, Xu C, Fan J, et al. Antibodies in Infants Born to Mothers With COVID-19 Pneumonia. *JAMA : the journal of the American Medical Association.* 2020;323(18):1848-1849.
12. Chien M, Anderson TK, Jockusch S, et al. Nucleotide Analogues as Inhibitors of SARS-CoV-2 Polymerase, a Key Drug Target for COVID-19. *J Proteome Res.* 2020;19(11):4690-4697.
13. Elfiky AA. Ribavirin, Remdesivir, Sofosbuvir, Galidesivir, and Tenofovir against SARS-CoV-2 RNA dependent RNA polymerase (RdRp): A molecular docking study. *Life Sci.* 2020;253:117592.

14. de Salazar PM, Ramos J, Cruz V, Polo S, del Amo J, Martinez-Salazar J. Tenofovir and remdesivir ensemble docking with the SARS-CoV-2 polymerase and template-nascent RNA [preprint]. 2020; http://hdl.handle.net/10261/220537. Accessed August, 2020.
15. Park SJ, Yu KM, Kim YI, et al. Antiviral Efficacies of FDA-Approved Drugs against SARS-CoV-2 Infection in Ferrets. *mBio.* 2020;11(3).
16. Del Amo J, Polo R, Moreno S, et al. Incidence and Severity of COVID-19 in HIV-Positive Persons Receiving Antiretroviral Therapy : A Cohort Study. *Annals of internal medicine.* 2020;173(7):536-541.
17. Del Amo J, Polo R, Moreno S, et al. Antiretrovirals and Risk of COVID-19 Diagnosis and Hospitalization in HIV-Positive Persons. *Epidemiology.* 2020;31(6):e49-e51.
18. Davies MA. HIV and risk of COVID-19 death: a population cohort study from the Western Cape Province, South Africa [Preprint]. 2020; 2020/07/09:https://www.ncbi.nlm.nih.gov/pubmed/32637972. Accessed August, 2020.
19. National Institutes of Health USNLoM. Randomized Clinical Trial for the Prevention of SARS-CoV-2 Infection (COVID-19) in Healthcare Personnel (EPICOS). 2020; https://clinicaltrials.gov/ct2/show/NCT04334928?cond=Randomized++clinical+trial+for+the+prevention+of+SARS-CoV-2+infection+%28+COVID19%29+in+healthcare+personnel. Accessed August 2, 2020.
20. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Final Report. *The New England journal of medicine.* 2020;383(19):1813-1826.
21. Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. *JAMA : the journal of the American Medical Association.* 2020;324(11):1048-1057.
22. Palmsten K, Huybrechts KF, Mogun H, et al. Harnessing the Medicaid Analytic eXtract (MAX) to Evaluate Medications in Pregnancy: Design Considerations. *PloS one.* 2013;8(6):e67405.
23. Rough K, Sun JW, Seage GR, 3rd, et al. Zidovudine use in pregnancy and congenital malformations. *AIDS.* 2017;31(12):1733-1743.
24. Brogly SB, Abzug MJ, Watts DH, et al. Birth defects among children born to human immunodeficiency virus-infected women: pediatric AIDS clinical trials protocols 219 and 219C. *The Pediatric infectious disease journal.* 2010;29(8):721-727.
25. Knapp KM, Brogly SB, Muenz DG, et al. Prevalence of congenital anomalies in infants with in utero exposure to antiretrovirals. *The Pediatric infectious disease journal.* 2012;31(2):164-170.
26. Williams PL, Crain MJ, Yildirim C, et al. Congenital anomalies and in utero antiretroviral exposure in human immunodeficiency virus-exposed uninfected infants. *JAMA pediatrics.* 2015;169(1):48-55.

27. Sibiude J, Mandelbrot L, Blanche S, et al. Association between prenatal exposure to antiretroviral therapy and birth defects: an analysis of the French perinatal cohort study (ANRS CO1/CO11). *PLoS Med.* 2014;11(4):e1001635.
28. Cooper E, Charurat M, Mofenson L, et al. Combination antiretroviral strategies for the treatment of pregnant HIV-1-infected women and prevention of perinatal HIV-1 transmission. *J Acquir Immune Defic Syndr.* 2002;29(5):484-494.
29. Fowler MG, Qin M, Fiscus SA, et al. Benefits and Risks of Antiretroviral Therapy for Perinatal HIV Prevention. *The New England journal of medicine.* 2016;375(18):1726-1737.
30. Phiri K, Fischer MA, Mogun H, et al. Trends in Antiretroviral Drug Use During Pregnancy Among HIV-Infected Women on Medicaid: 2000-2007. *AIDS patient care and STDs.* 2014;28(2):56-65.
31. Rough K, Seage GR, 3rd, Williams PL, et al. Birth Outcomes for Pregnant Women with HIV Using Tenofovir-Emtricitabine. *The New England journal of medicine.* 2018;378(17):1593-1603.
32. Cooper WO, Hernandez-Diaz S, Gideon P, et al. Positive predictive value of computerized records for major congenital malformations. *Pharmacoepidemiology and drug safety.* 2008;17(5):455-460.
33. Palmsten K, Huybrechts KF, Kowal MK, Mogun H, Hernandez-Diaz S. Validity of maternal and infant outcomes within nationwide Medicaid data. *Pharmacoepidemiology and drug safety.* 2014;23(6):646-655.
34. He M, Huybrechts KF, Dejene SZ, et al. Validation of algorithms to identify adverse perinatal outcomes in the Medicaid Analytic Extract database. *Pharmacoepidemiology and drug safety.* 2020;29(4):419-426.
35. Phiri K, Hernandez-Diaz S, Dugan KB, et al. First trimester exposure to antiretroviral therapy and risk of birth defects. *The Pediatric infectious disease journal.* 2014;33(7):741-746.
36. Desai RJ, Rothman KJ, Bateman BT, Hernandez-Diaz S, Huybrechts KF. A Propensity-score-based Fine Stratification Approach for Confounding Adjustment When Exposure Is Infrequent. *Epidemiology.* 2017;28(2):249-257.
37. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry Interim Report for 1 January 1989 through 31 July 2019. 2019; www.APRegistry.com. Accessed August, 2020.
38. Floridia M, Mastroiacovo P, Tamburrini E, et al. Birth defects in a national cohort of pregnant women with HIV infection in Italy, 2001-2011. *BJOG : an international journal of obstetrics and gynaecology.* 2013;120(12):1466-1475.
39. Brown RS, Jr., McMahon BJ, Lok AS, et al. Antiviral therapy in chronic hepatitis B viral infection during pregnancy: A systematic review and meta-analysis. *Hepatology.* 2016;63(1):319-333.
40. Siberry GK, Jacobson DL, Kalkwarf HJ, et al. Lower Newborn Bone Mineral Content Associated With Maternal Use of Tenofovir Disoproxil Fumarate During Pregnancy. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2015;61(6):996-1003.

41. Salvadori N, Fan B, Teeyasoontranon W, et al. Maternal and Infant Bone Mineral Density 1 Year After Delivery in a Randomized, Controlled Trial of Maternal Tenofovir Disoproxil Fumarate to Prevent Mother-to-child Transmission of Hepatitis B Virus. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2019;69(1):144-146.
42. World Health Organization. Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection. World Health Organization;. *http://wwwwhoint/hiv/pub/arv/arv-2016/en/ Accessed July 27, 2016.* 2016.
43. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. 2016; https://aidsinfo.nih.gov/guidelines/html/3/perinatal-guidelines/0. Accessed Accessed July 27, 2016.
44. Heinke D, Rich-Edwards JW, Williams PL, et al. Quantification of selection bias in studies of risk factors for birth defects among livebirths. *Paediatric and perinatal epidemiology.* 2020;34(6):655-664.
45. Bateman BT, Gagne JJ. The Obstetric Comorbidity Index predicts severe maternal morbidity. *BJOG : an international journal of obstetrics and gynaecology.* 2015;122(13):1756.

Table 1 Baseline characteristics for pregnant women living with HIV and receiving antiretroviral therapy during the first trimester in Medicaid Analytic eXtract 2000-2014.

Characteristics	Unadjusted					Adjusted through PS stratification[a]				
	TDF (n=872)		Unexposed (no TDF, but ART in T1) (n=1,033)		StDiff	TDF (n=866)		Unexposed (no TDF, but ART in T1) (n=1,020)		StDiff
	No.	%	No.	%		No.	%	No.	%	
Age[b]	29.1 (6.2)		28.1	(6.1)	0.174	29.1	(6.2)	29.5	(6.2)	-0.056
Race										
White	121	13.9	160	15.5	-0.046	121	14.0	127	12.5	0.044
Black/African American	550	63.1	689	66.7	-0.076	545	62.9	645	63.3	-0.007
Hispanic/Latino	22	2.5	52	5.0	-0.132	22	2.5	36	3.5	-0.056
Other/Unknown	179	20.5	132	12.8	0.209	178	20.6	212	20.8	-0.006
Region										
Northeast	427	49.0	373	36.1	0.262	423	48.9	534	52.3	-0.070
Midwest	156	17.9	165	16.0	0.051	155	17.9	150	14.7	0.088
South	234	26.8	425	41.1	-0.305	233	26.9	251	24.6	0.052
West	55	6.3	70	6.8	-0.019	55	6.4	86	8.4	-0.078
Maternal conditions [c]										
Diabetes	25	2.9	53	5.1	-0.116	25	2.9	30	2.9	-0.003
Obesity or overweight	42	4.8	34	3.3	0.077	42	4.9	49	4.9	0.000
Anemia	70	8.0	72	7.0	0.040	69	8.0	87	8.6	-0.021
Depression	125	14.3	119	11.5	0.084	124	14.3	144	14.1	0.007
Anxiety	45	5.2	34	3.3	0.093	45	5.2	51	5.0	0.008
Bipolar disorder	39	4.5	22	2.1	0.131	39	4.5	44	4.3	0.010
Alcohol abuse or dependence	35	4.0	26	2.5	0.084	34	3.9	39	3.8	0.006
Drug abuse or dependence	79	9.1	64	6.2	0.108	78	9.0	100	9.8	-0.026
Tobacco use	41	4.7	36	3.5	0.061	40	4.6	45	4.4	0.009
Pain	152	17.4	153	14.8	0.071	150	17.3	170	16.6	0.018

Migraine/ headache	59	6.8	80	7.7	-0.038	58	6.7	80	7.8	-0.044
Viral hepatitis B	<11[e]	1.2	<11[e]	0.2	0.117	<11[e]	0.6	<11[e]	0.6	-0.005
Hepatitis C	22	2.5	13	1.3	0.093	21	2.4	26	2.6	-0.010
Herpes simplex virus	29	3.3	24	2.3	0.061	29	3.4	32	3.1	0.012
Sexually transmitted infection	50	5.7	73	7.1	-0.054	50	5.8	61	5.9	-0.007
Concomitant medications										
Antidepressants	153	17.6	170	16.5	0.029	151	17.4	181	17.7	-0.007
Anticonvulsants	57	6.5	42	4.1	0.110	56	6.5	92	9.0	-0.096
Antibiotics	543	62.3	637	61.7	0.012	538	62.1	643	63.0	-0.018
Fluconazole	151	17.3	138	13.4	0.110	150	17.3	170	16.6	0.019
Trimethoprim	205	23.5	198	19.2	0.106	202	23.3	234	22.9	0.009
Suspected teratogens	23	2.6	20	1.9	0.047	23	2.7	25	2.5	0.011
Markers of burden of illness [d]										
Maternal comorbidity index[45] [b]	3.96(2.3)		3.60(2.1)		0.168	3.96(2.3)		4.08(2.3)		-0.053
N distinct diagnoses [b]	4.49(4.0)		3.97(3.8)		0.135	4.46(3.9)		4.51(4.0)		-0.011
N non-ART prescription drugs [b]	3.53(3.6)		3.03(3.4)		0.140	3.52(3.6)		3.65(3.7)		-0.035
N HIV-related procedures [b]	0.05(0.2)		0.02(0.1)		0.170	0.05(0.2)		0.05(0.2)		0.013
N outpatient visits [b]	3.36(5.0)		2.70(4.6)		0.137	3.34(4.9)		3.70(8.4)		-0.052
Number of ART medications										
N distinct ART drugs <4	167	19.2	569	55.1	-0.801	167	19.3	194	19.0	0.008
N distinct ART drugs = 4	407	46.7	377	36.5	0.208	407	47.0	502	49.2	-0.044
N distinct ART drugs > 4	298	34.2	87	8.4	0.662	292	33.7	325	31.8	0.040
Specific ART medications										
Didanosine	48	5.5	40	3.9	0.077	46	5.3	37	3.6	0.082
Efavirenz	158	18.1	69	6.7	0.352	158	18.2	89	8.7	0.282
Emtricitabine	743	85.2	<11[e]	0.8	3.263	737	85.1	<11[e]	0.9	3.237
Lamivudine	202	23.2	957	92.6	-1.979	201	23.2	967	94.8	-2.122
Lopinavir	224	25.7	300	29.0	-0.075	220	25.4	508	49.8	-0.520
Nelfinavir	30	3.4	253	24.5	-0.637	30	3.5	160	15.7	-0.425
Nevirapine	42	4.8	151	14.6	-0.335	42	4.9	98	9.6	-0.185
Raltegravir	80	9.2	15	1.5	0.349	78	9.0	18	1.7	0.326

Ritonavir	641	73.5	403	39.0	0.741	635	73.3	711	69.7	0.081
Zidovudine	174	20.0	850	82.3	-1.594	173	20.0	808	79.3	-1.472

Abbreviations: TDF, tenofovir disoproxil fumarate; ART, antiretroviral therapy; N, number; SD, standard deviation; StDiff, standardized difference.

a Given the PS stratification, the counts for the unexposed group are weighted counts to demonstrate the balance in baseline covariates

b Values are expressed as mean (standard deviation)

c Maternal conditions and concomitant medication use were measured from 3 months before the start of pregnancy through the end of the first trimester.

d General markers of the burden of illness (except for the number of distinct ART drugs) were measured during the 3 months before but not during pregnancy, as these measures may be affected by early detection of pregnancy complications

e Cell size <11 for MAX cohort are suppressed in accord with the CMS cell size suppression policy.

Table 2. Risk of congenital malformations in infants born to women living with HIV and receiving antiretroviral therapy during the first trimester in Medicaid Analytic eXtract 2000-2014.

Exposure group	Events, N of affected infants	Total N of pregnancies	Risk, N/100 pregnancies	(95% CI)	Relative risk	(95% CI)
Unadjusted						
TDF	37	872	4.24	(2.91, 5.58)	1.15	(0.74, 1.80)
TDF + emtricitabine	31	743	4.17	(2.73, 5.61)	1.13	(0.71, 1.81)
ART without TDF	38	1,033	3.68	(2.53, 4.83)	1.00	Reference
Propensity score stratified						
TDF	37	866	4.27	(2.93, 5.62)	1.21	(0.77, 1.90)
TDF + emtricitabine	31	741	4.18	(2.74, 5.63)	1.14	(0.71, 1.82)
ART without TDF	38	1,020	3.73	(2.56, 4.89)	1.00	Reference

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; N, number; TDF, tenofovir disoproxil fumarate.

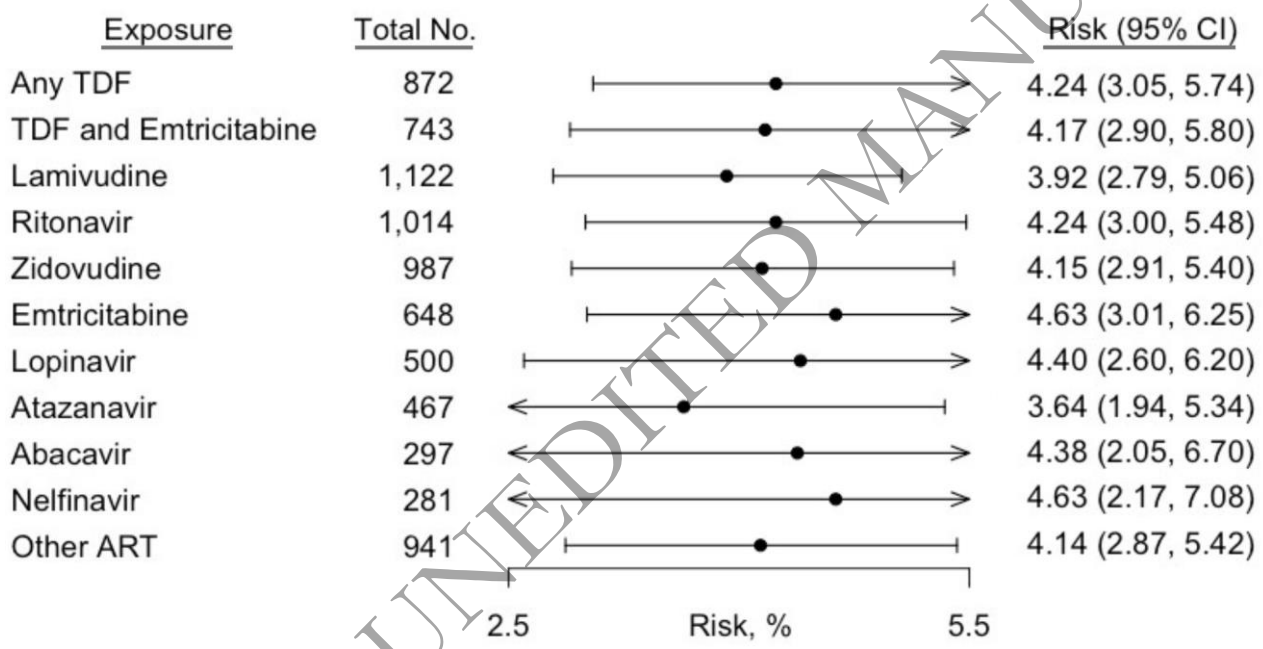
FIGURE LEGENDS

Figure 1. Prevalence of congenital malformations for the most common antiretrovirals used during the first trimester in Medicaid Analytic eXtract 2000-2014.

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; N, number; TDF, tenofovir disoproxil fumarate

Figure 2. Forest plot of meta-analysis results: relative risk of congenital malformations for tenofovir use early in pregnancy compared to antiretroviral therapy strategies not including tenofovir.

Abbreviations: APR, antiretroviral pregnancy registry; CI, confidence interval; N, number.



First Author, Year	Tenofovir		Reference		
(Reference No.)	No. of Events	Total No.	No. of Events	Total No.	RR (95% CI)
Brogly, 2010 (24)	4	45	40	718	1.60 (0.60, 4.26)
Knapp, 2012 (25)	11	138	22	379	1.37 (0.68, 2.76)
Floridia, 2013 (38)	5	173	18	547	0.88 (0.33, 2.33)
Sibiude, 2014 (27)	30	823	231	4,465	0.70 (0.49, 1.02)
Williams, 2015 (26)	32	431	61	788	0.96 (0.64, 1.45)
APR, 2019 (37)	97	4,005	187	6,115	0.79 (0.62, 1.01)
Current study	37	872	38	1,033	1.15 (0.74, 1.80)
Pooled					0.88 (0.75, 1.03)